UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,619	10/17/2003	Margot Mary O'Toole	WYE-029	9490

54623 7590 03/16/2006

KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP/WYETH
75 STATE STREET
BOSTON, MA 02109-1808

EXAMINER	
WONG, JENNIFER SHIN SHIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,619	O'TOOLE ET AL.	
	Examiner	Art Unit	
	Jennifer Wong	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *4 and 9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *February 23, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to the election filed January 11, 2006.

2. Claims 1-21 are pending. Applicant's election of Group I in the reply filed on January 11, 2006 is acknowledged.

3. Applicant's election of Invention I in the reply filed on January 11, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 9-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Upon initial examination, a further restriction was applied to Group I between antibody assays and assays measuring midkine RNA transcript levels. During a telephone conversation with Brian Fairchild on February 7, 2006, a provisional election was made to prosecute the invention of assays measuring midkine RNA transcript levels, claim 5.

In view of this further restriction requirement, the new groups are as follows:

I. Claim 4, drawn to methods to detect midkine gene expression levels, with antibodies, classified in class 435, subclass 7.1.

II. Claim 5, drawn to methods to measure midkine RNA expression levels, classified in class 435, subclass 6.

III. Claim 9-17, drawn to pharmaceutical compositions, classified in class 514, subclass 1.

IV. Claim 17, drawn to methods of administering pharmaceutical compositions, classified in 514, subclass 2.

V. Claims 18-19, drawn to methods drawn to identify midkine agonists 4, classified in class 435, subclass 7.1.

VI. Claim 20, drawn to methods to identify midkine modulators, classified in class 435, subclass 4.

VII. Claim 21, drawn to kits to diagnose lupus comprising nucleic acids, classified in class 536, subclass 23.1.

VIII. Claim 21, drawn to a kit to diagnose lupus comprising antibodies, classified in class 536, subclass 387.1.

With the new restriction requirement, claims 1-3, 6-8 link the invention of Groups I and II. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s). Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or

nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.0

5. Affirmation of this election must be made by applicant in replying to this Office action.

6. Claims 9-21 are is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. Claims 1-3, 5-8 are under examination.

Information Disclosure Statement

The information disclosure statement filed October 12, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it contains an international search report of PCT/US2004/005655. It has been placed in the application file, but the information referred to therein has not been considered as to the merits because it was not publicly available.

Claim Objections

3. Claim 2 is objected to because of the following informalities: a misspelling of control in the recitation "at least one contro sample" in lines 1 and 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing lupus nephritis (LN) in a mouse wherein the method comprises: 1) obtaining a kidney sample from a control mouse and a mouse with LN; 2) determining the mRNA transcript level of midkine, 3) comparing mRNA transcript level of midkine between a control and mouse with LN, wherein an increase in midkine mRNA transcript level, relative to the control, indicates that said mouse has an increased likelihood of LN does not reasonably provide enablement for methods to diagnose systemic lupus erythematosus (SLE) or LN in any mammal by midkine expression level relative of the midkine expression level in a normal population. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims

The claims are broadly drawn to methods to detect midkine expression levels from biological samples by comparing midkine levels of controls and mammals with systemic lupus erythematosus (SLE) or lupus nephritis (LN). The claims are drawn towards detecting the presence, absence, upregulation or downregulation of midkine expression in any biological sample of any mammal. The claims include the analysis of midkine levels of monkeys, sheep, dogs, pandas, lions, cows, cats, horses, in any bodily sample such as cerebrospinal fluid, saliva, effusions, blood, gastrointestinal secretions, and tissues such as brain, stomach, lung, cardiac, epithelial, ocular, intestinal, liver, and stomach to detect midkine expression and its relationship to lupus.

Nature of the Invention

The invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification

The specification teaches systematic lupus erythematosus (SLE) is an autoimmune disease that has diverse and variable clinical manifestations that range from skin rash and joint pain that can show spontaneous remissions to severe kidney disease that may result in renal failure, otherwise known as lupus nephritis (LN). Midkine (MDK) has several functions including neural-glial interactions in brain

development, inflammation, tumor and angiogenesis, and anti-apoptotic activities (specification, pages 14-19). The specification asserts that midkine is a marker for SLE or LN, and its expression can be utilized as a diagnostic for said diseases (page 4). The specification concludes "MDK has not previously been associated with SLE and LN.....While mouse models were used for the initial differentiation expression analysis, it is well-appreciated that animal models can be interpreted to reflect expression levels from human subjects as well. The present invention...encompasses human MDK" (page 22). The specification further asserts "without limitation as to mechanism, the present invention is based in part on the principle that modulation of the expression of the MDK gene expression may ameliorate SLE/LN, when they are expressed at levels similar or substantially similar to normal non-diseased tissues" (page 23).

The specification discloses working examples of the isolation of RNA from kidney samples of several different mouse models of lupus that ranged in age of five months to 8, 16, 20 weeks of age, thus representing early, intermediate, and late stages of lupus, and control mice of the same age range. The working examples disclose that after the isolation of kidney tissues from said mice, RNA was isolated and cDNA was synthesized, and then the samples were analyzed with Affymetrix Mu11KsubA and Mu11KsubB microarrays. Statistical analysis was subsequently performed, and TaqMan assays were performed on genes of interest (pages 13-14 and 78-82).

State of the Prior Art

The art acknowledges midkine is a ubiquitous gene that plays an integral component in many cellular pathways and it is expressed in several tissues. Midkine is

a member of heparin-binding growth/differential factor family and plays a role during development (Zhang, Current Opinion in Hematology, 1999, Vol. 6, No. 1, page 44 [pages 1-13 in printed HTML article]). Zhang teaches midkine is expressed during embryogenesis in neural development and it is mitogenic in some cell lines (page 7, and Takada et al., Journal of Biochemistry, 1997, Vol. 122, pages 453-458). In adults, midkine plays a role in neural repair and regeneration as it is expressed in response to neural injury, Alzheimer's plaques, and prevents retinal degeneration due to prolonged sun exposure (Zhang, page 7). Sato et al (Journal of Immunology, 2001, Vol. 167, pages 3463-3469) teaches midkine enhances migration of inflammatory cells in response to renal injuries. Despite its varied role, normal midkine expression in humans is tissue specific. Tsutsui et al teaches (Cancer Research, 1993, Vol. 53, pages 1281-1285) "in normal tissues, MK is weakly expressed in the kidney....lung alveoli... mucosal tissues of the stomach... colon..., and spleen, ...moderately in the thyroid...and highly in the mucosal tissue of the small intestine....No MK mRNA was detected in the liver" (page 1282, Figure 1).

Lupus is an autoimmune disease that is characterized by joint pain, rash, weakness, and primarily affects women (Kotzin, Cell, 1996, Vol. 85, pages 303-306). The underlying cause of lupus has yet to be determined as environmental factors such as sun exposure, viral or bacterial infections, hormonal and drug treatments, and genetic contributions play a role in the manifestation of the disease (Kotzin, page 305). Kotzin teaches several animal models have been used to study lupus, however, due to the complex nature of the disease, "even when one animal model and one phenotype is

considered, the genetic basis of lupus-like disease is remarkably complex, involving contributions from multiple genes in addition to class II MHC....Furthermore, it seems likely that different genetic contributions are operative in different animal models (and therefore in different patients), even when the same phenotype is being followed" (page 305). Kotzin further teaches mouse models are used to study the genetic causes of lupus, and to predict human genes that are associated with said disease since mouse and human genes are homologous (Journal of Clinical Investigation, 1997, Vol.99, No. 4, pages 557-558). However, as stated above, environmental factors and phenotypic expression of lupus have considerable variation, and since the environment conditions are controlled for animal studies and the animal models are bred to have uniform lupus symptoms, it is unclear if results from animal studies can be applicable to humans. Kotzin teaches, "disease phenotype among mice in each cross is much more uniform compared to the relatively heterogeneous disease expression in patients. Especially in SLE, clinical manifestations and autoantibody production can be extremely diverse and variable, which is in part genetically based, and this variability can confound genetic studies" (Journal of Clinical Investigation, page 557). To ensure accurate predictions of the results of mouse lupus models to humans "there should also be concern that an initial mapping in a complex trait reflects false positive readings....If true, this human locus...may not be in a region synthenic to the murine susceptibility locus, and linkage in the current human study would therefore represent quite a fortuitous finding," and in order to ensure accurate results, large studies of human patients will need to be performed (Kotzin, Journal of Clinical Investigation, page 558).

The Relative Skill of Those in the Art

The level of skill in the art is deemed to be high.

The Predictability or Unpredictability of the Art and Degree of Experimentation

The art is extremely unpredictable with regard to midkine's expression levels in any biological sample of any mammal. Tsutsui teaches that normal levels of midkine are different among human tissues. With non-uniform levels of midkine in tissues, it is unpredictable how midkine's expression level relative to controls of specific tissues can be extrapolated to midkine levels of different tissues to detect lupus. Further, the specification is silent about the range or level of wildtype or variant midkine expression is needed to diagnose SLE or LN. While the skilled artisan can individually determine tissue or sample specific midkine's expression by its presence, absence, upregulation or downregulation in natural state, and compare it midkine's presence, absence, upregulation or downregulation in the same and/or different samples of a diseased mammal, and quantitate the threshold or midkine's range level that is necessary to diagnose lupus such further research is unpredictable and undue. For instance, as Tsutsui teaches above, midkine is not expressed in liver tissues, and it is moderately expressed in the thyroid. It is unpredictable if the upregulation of midkine in the liver can predict lupus if there is no midkine expression in thyroid samples, and if in said example, the levels can be extrapolated to different tissues, it is unpredictable if a 2-fold, or 10-fold level difference can predict lupus. The specification has taught elevated levels of midkine expression in kidney samples can predict LN in mice, however, it is silent about the midkine levels in the remaining biological samples in other mammals

that can predict SLE or LN. Moreover, as indicated by Kotzin, an animal model may not be an accurate representation of another animal's response to lupus. Genetic homology does not necessarily correlate to phenotypic expression. As mentioned previously, environmental factors play a role in the development of lupus, and it is unpredictable if a mouse, particularly in a controlled environment, will react in the same manner to environmental factors as humans. Consequently, it is unpredictable if a mouse phenotypic expression of lupus will be similar to humans. Consequently, the skilled artisan would have to examine midkine's expression in any biological samples of any mammal in order to diagnose lupus. Due to the absence of information regarding other mammalian levels of midkine in various samples, it is highly unpredictable if the presence and absence of midkine and its range of upregulation or downregulation can predict SLE or LN as each mammal and biological sample with the exception of increased midkine expression levels in mouse kidney samples of LN, would have to be individually examined. In view of the quantity of experimentation of detecting midkine expression in any biological sample in any mammal, and determining if its presence or absence, upregulation or downregulation of wildtype or variant form is a lupus marker as well as unknown genetic and environmental variables that cause lupus, reliability mouse models, it is unpredictable if midkine expression levels can be used to diagnose lupus in any biological sample of any mammal. As a result, the specification does not teach the person skilled in the art how to reasonably predict, without undue burden, SLE or LN by midkine expression levels in biological sample of any mammal.

Amount of Direction or Guidance Provided by the Specification

There are no sufficient teachings or quantitative data that describe possible combinations of mRNA levels of midkine expression, its presence or absence, and range of upregulation and downregulation of its wildtype or variant form, in any biological samples of any mammal that can detect SLE or LN other than elevated mRNA transcript levels of midkine in a mouse with LN in kidney samples. The specification does not teach any threshold level of midkine expression is needed to predict lupus, and if the value is species specific and/or specific to biological samples. Further, the specification does not teach if mutant midkines can also diagnose lupus, consequently, the skilled artisan would not know which specific mutant, a splice variant or single nucleotide polymorphism, for example, and its exact mutation, is needed to prognose lupus. As a result, the skilled artisan would not know if the absence, presence, upregulation or downregulation of wildtype or mutant midkine is necessary to predict lupus and at which stage. The skilled artisan can individually examine any tissue, blood, or urine sample in any mammal such as monkeys, sheep, dogs, pandas of any bodily sample such as cerebrospinal fluid, urine, saliva, and tissues such as brain, stomach, lung, and liver to detect midkine expression and its relationship to lupus, the outcome of such research cannot be predicted. The specification does not teach the person skilled in the art how to reasonably predict, without undue

burden, methods of detecting LN with the exception of elevated midkine levels in mouse kidney samples.

Working Example

The specification does not provide working examples of methods to diagnose lupus with midkine expression levels in any biological sample of any mammal afflicted with lupus except for elevated levels of midkine in mouse kidneys. The methods do not demonstrate the methodology can be used to predictably diagnose lupus with any midkine transcript levels of any biological sample in any mammal except for mouse kidney samples.

Conclusions

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genentech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In view of the high level of unpredictability in the art

and lack of guidance provided by the specification and prior art, undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 6, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Mishima et al (Neuroscience Letters, 1997, Vol. 233, pages 29-32).

Mishima teaches methods to detect midkine (MK) expression levels comprising the steps of: 1) isolating biological samples from patients; 2) detecting MK expression levels with Northern blots analysis; and 3) comparing said expression level to control samples. In particular, Mishima measures MK expression levels in human astrocytomas, a tissue specific brain cancer, with controls, and teaches MK expression level is associated with malignant progression of astrocytomas (page 29). Accordingly, Kato teaches methods to detect MK expression levels. In the absence of information regarding the source of the non-neoplastic tissue samples, it is interpreted that control patients from which the tissues were isolated from did not have SLE or LN.

With respect to claims 1, 2, 5, 6, Mishima teaches "tissue specimens of nine glioblastomas, four anaplastic astrocytomas, and seven low-grade astocytomas" were obtained, and "total RNA was extracted from tissue specimens" (page 30, claim

limitation 6). In order to "to quantify the expression of MK mRNA in human astrocytomas, we performed Northern blot hybridization" from low and high grade astrocytomas, glioblastomas as well as controls "using cDNA encoding human MK as a probe " (pages 29, right column, last line through page 30, first paragraph and Figures 1A, and Table 1; claim limitations 1 and 5).

With respect to claim 8, Mishima teaches samples were "from human astrocytoma tissues" with "informed consent" from patients (page 30, left column, first paragraph, claim limitation 8).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swiniarski et al (FASEB Journal, March 2001, Vol. 15, No. 5, page A1214) in view of Takada et al. (Journal of Biochemistry, 1997, Vol. 122, pages 453-458) in further view of Affymetrix GeneChip Murine 11K set (Product manual, 1998).

Swiniarski teaches methods to detect expression levels in systemic lupus erythematosus mouse models and controls of different ages utilizing microarrays. Swiniarski teaches "(NZBxNZW)F1 mice develop a severe autoimmune disease that resembles human systemic lupus erythematosus. Utilizing Affymetrix oligonucleotide

arrays containing approximately 11,000 murine genes, we have compared the gene expression levels of kidney mRNA from young...asymptomatic mice and older...disease mice. An expression profile of genes differentially regulated in disease free and diseased kidney was identified. Among these disease associated genes are many consistent with the physiology of the disease. These include genes related to T and B lymphocyte function, antigen processing and presentation, complement, and fibrosis" and the "expression levels of the vast majority of these genes were not significantly different between young and old C57BL/6 mice...the expression differences observed in the diseased strain were not due to normal age related changes in the kidney" (page A1214, claim limitations 2, 3, 5-7). However, Swiniarski does not teach the study of midkine expression levels.

Takada teaches midkine is associated inflammation associated expression in arthritic patients. Takada teaches elevated levels of midkine are significantly expressed in arthritic patients as compared to controls which did not express midkine (page 456). Takada further teaches "midkine is also known to promote fibrinolysis" (page 453).

Affymetrix teaches a Murine 11K set wherein "oligonucleotide probes are synthesized on the arrays complementary to a portion of each gene or exemplar represented. On the Murine 11K set, there are approximately 20 oligonucleotide probe pairs for each sequence" (page 1). Within the Murine 11K set, there are two probe arrays Mu11KsubA and Mu11KsubB, each array containing 1 and 5 midkine probe sets respectively.

It would have been prima facie obvious at the time the invention was made to have modified the methods of Swiniarski with Affymetrix's microarrays to detect midkine levels in lupus patients. Swiniarski teaches methods to detect expression levels in diseased and control lupus animal models with kidney samples when studying the immune response, inflammation, and fibrosis, whereas Affymetrix teaches a murine microarray with 11,000 genes, including midkine. One skilled in the art at the time the invention was made would have been motivated to have used Affymetix's Murine 11K Set because Swiniarski teaches Affymetrix arrays can be utilized to detect gene expression in an immune response, and one skilled in the art would have used Affymetrix's Murine 11K Set in order to achieve the benefit of a high throughput, cost effective method to study gene expression levels of lupus in animal models. The skilled artisan would have been motivated to have utilized Affymetrix's Murine 11K Set as it "allows one to monitor the relative abundance of greater than 11,000 mRNA transcripts" (page 1). Affymetrix also teaches that the probe arrays can be used for gene expression research purposes, including midkine, with the analysis of thousands of genes, the skilled artisan can easily screen a multitude of genes that are associated with lupus without individually examining the expression level of an immense number of genes.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Wong whose telephone number is (571) 272-1120. The examiner can normally be reached on Monday-Friday; 8 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Wong

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER